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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,804	02/22/2002	Lisa C. McConlogue	MBHB02-329-A	2073

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EXAMINER	
CROUCH, DEBORAH	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,804	MCCONLOGUE ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,9,13-28,30-39 and 42-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,9,13-28,30-39 and 42-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments filed February 10, 2006 have been fully considered but they are not persuasive. The amendment has been entered.

The rejection made in the office action mailed August 10, 2005 under 35 U.S.C. § 101 is withdrawn in view of applicant's arguments.

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25 and 26 remain rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility for reasons set forth in the rejection mailed June 28, 2004.

Claims 25 and 26 are to methods of analyzing potential side-effects for an inhibitor of β-secretase comprising exposing a transgenic mouse comprising at least one non-functional allele of BACE-1 or cortical culture derived from the mouse to an inhibitor of BACE-1 and measuring whether there is a change in at least one component of the transgenic mouse or cortical cell culture responsive to the inhibitor.

This method lacks patentable utility because any mouse or any cortical cell culture could be used to make the claimed measurement. A BACE-1 knockout mouse or a cortical cell culture from the mouse is not required for the measurements to be made. There is no particular need for any particular mouse especially since no component associated with Alzheimer's disease is being measured.

Claims 1-6, 9 and 13-52 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1, 2, 5, 6, 9, 13-28, 30-39 and 42-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome is homozygous for nonfunctional alleles of a β-secretase-1 (BACE-1) gene, wherein the allele is rendered nonfunctional by deletion of exons 4-8, wherein the mouse lacks functional BACE-1 and the mouse further comprising a transgene integrated into its genome comprising a DNA sequence encoding an APP with a familial Alzheimer's disease mutation operably linked to a promoter; cortical cell cultures derived from the mouse, where the cells lack functional BACE-1, and wherein the cell culture comprises a detectable amount of an amyloid peptide recognized by an antibody that recognizes residues 13-28 of Aβ;

methods for screening for an inhibitor of the production by a protease other than BACE-1 of an amyloid peptide recognized by an antibody that recognizes residues 13-28 of Aβ comprising exposing a transgenic mouse whose genome is homozygous for nonfunctional alleles of a β-secretase-1 (BACE-1) gene, wherein the allele is rendered nonfunctional by deletion of exons 4-8, wherein the mouse lacks functional BACE-1 or cortical cell culture derived from the mouse, where the cells lack functional BACE-1 to an agent and detecting the amyloid peptide produced by detection with an antibody that recognizes residues 13-28 of Aβ, wherein a reduced amount of amyloid peptide produced in the exposed transgenic mouse or cell culture relative to a transgenic mouse whose genome is homozygous for nonfunctional alleles of a β-secretase-1 (BACE-1) gene, wherein the allele is rendered nonfunctional by deletion of exons 4-8, wherein the mouse lacks functional BACE-1 or a cortical cell culture derived from the mouse, which has not been exposed to the agent is indicative of inhibitory activity of using the homozygous mouse;

methods of analyzing potential side-effects for an inhibitor of β-secretase comprising exposing a transgenic mouse whose genome is homozygous for nonfunctional alleles of a β-secretase-1 (BACE-1) gene, wherein the allele is rendered nonfunctional by deletion of exons 4-8, wherein the mouse lacks functional BACE-1 or a cortical cell culture derived from the mouse to an inhibitor of β-secretase; and measuring whether there is a change in the level of at least one component of the transgenic mouse or cortical cell in response to the administration of the inhibitor, wherein a change in the level of at least one component indicates a potential side effect;

a method for generating a transgenic mouse whose genome is homozygous for nonfunctional alleles of a β-secretase-1 (BACE-1) gene, wherein the mouse lacks functional BACE-1, wherein mice heterozygous for the deletion are bred to produce mice homozygous for BACE-1 deletions; and where the genome of the mouse further comprises a transgene encoding a mutant APP associated with familial Alzheimer's disease; a cortical cell culture derived from the mouse, and wherein the cell culture comprises a detectable amount of an amyloid peptide recognized by an antibody that recognizes residues 13-28 of Aβ, does not reasonably provide enablement for the claims as written. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The methods of assay for an inhibitor of the production by a protease other than BACE-1 of an amyloid peptide recognized by an antibody that recognizes residues 13-28 of Aβ requires the mouse to be homozygous for BACE-1 disruption. Only in the homozygous mouse could one identify an inhibitor of another enzyme with BACE-1 activity. If BACE-1 were present, then there would be confusion as to the enzyme being inhibited. Further, methods of analyzing potential side effects for an inhibitor of β-secretase.

The specification does not enable another peptide recognized by antibodies to residues 13-28 of Aβ (see claims 21, 22, 52-55). The disclosed use of the mouse is in relation to the production of Aβ, the peptide associated with Alzheimer's disease. Thus, the only peptide enabled to be detected by Aβ antibodies is the Aβ peptide or β-amyloid peptide. This would be true even if applicant's mouse permitted the finding of an inhibitor of Aβ formation by an enzyme other than BACE-1 (see specification, page 5, parag. 27). The only peptide or protein enabled to be detected by an antibody recognizing residues 13-28 of Aβ is Aβ or β-amyloid.

The BACE-1 knockout mouse is further disclosed to contain in its genome a DNA sequence encoding an FAD APP (see claims 13-16 and 46-49). However, the claims do not require the DNA sequence to be operably linked to a promoter or integrated into the genome. The specification only enables the production of the double-transgenic mouse where a promoter regulates expression of the FAD-APP DNA sequence. Furthermore, proper distribution of the FAD-APP DNA sequence, the DNA sequence must be integrated into the genome. An extrachromosomal DNA sequence will not necessarily be present in all cells of the mouse because replication and division will not be coordinated with that of the cells.

Claims 25 and 26 are to methods of analyzing potential side-effects for an inhibitor of β-secretase comprising exposing a transgenic mouse comprising at least one non-functional allele of BACE-1 or cortical culture derived from the mouse to an inhibitor of BACE-1 and measuring whether there is a change in at least one component of the transgenic mouse or cortical cell culture responsive to the inhibitor. However, these claims are not enabled as there is no guidance in the specification as to what parameter is being measured. The specification requires the reader to invent the parameter. In particular, the specification states "a plurality of mRNA species" but does not provide guidance as to what RNA species are to be measured.

Thus, the skilled artisan would need to engage in an undue amount of experimentation to implement the claimed invention without a predictable degree of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 34 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 sates "a blastocyst formed by differentiation of a mouse embryonic stem cell." It is not clear what applicant is trying to claim, as a blastocyst according to the invention is vehicle for forming a chimeric mouse. The ES cells comprising the altered BACE-1 gene is injected into a blastocyst to produce a chimeric mouse whose genome comprises a deletion of in exons 4-8 in the BACE-1 genomic sequence. The invention as disclosed in the specification is not reflected in claim 34. Applicant could amend claim 34 to state a blastocyst comprising the mouse ES cell of claim 27.

Claim 35, step 4 states "breeding the chimeric mice with mice or the type which provided the blastocysts." This is confusing as type could be breed, age, or any phenotype or genotype. The metes and bounds of the claim are not clear.

Claim 52 does not further limit claims 38. Claim 52 is to cortical cells, whereas claim 38 is to a mouse.

The claims are free of prior art.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 7:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

April 21, 2006